Breast Cancer Incidence in Women Prenatally Exposed to Maternal Cigarette Smoke

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Background: Clinical studies show that maternal cigarette smoking reduces pregnancy estrogen levels. Women prenatally exposed to maternal cigarette smoke may, therefore, have a lower breast cancer risk because the fetal mammary gland's exposure to maternal estrogen is decreased. Associations between prenatal maternal cigarette smoke exposure and breast cancer, however, have not been observed in previous case–control studies that relied on exposure assessment after the onset of cancer. At the start of this study, cigarette smoking history was obtained directly from the mother.

Methods: The National Cooperative DES Adenosis project was a follow-up study of health outcomes in women prenatally exposed to diethylstilbestrol (DES). At the start of the study, women's mothers provided information about cigarette smoking habits during the time they were pregnant with the study participant. In the current study, the breast cancer rates are compared among 4031 women who were or were not prenatally exposed to maternal cigarette smoke. The resultant relative rate (RR) is adjusted for potential confounding by other breast cancer risk factors using Poisson regression modeling.

Results: Fetal exposure to maternal cigarette smoke appeared to be inversely associated with breast cancer incidence (RR = 0.49; 95% confidence interval [CI] = 0.24–1.03). The inverse association was more apparent among women whose mothers smoked 15 cigarettes or fewer per day than among daughters of heavier smokers. There were, however, too few cases to precisely estimate a possible dose-response relationship.

Conclusion: These results support the hypothesis that in utero exposure to maternal cigarette smoke reduces breast cancer incidence.

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Trichopoulos[1] hypothesized that fetal exposure to maternal pregnancy estrogens may influence subsequent breast cancer risk. Cigarette smoking is among the factors believed to affect a woman's pregnancy hormone levels. Investigators have observed a small reduction in total serum pregnancy estrogen levels among light-smoking women compared with women who never smoked in their lives.[2] More pronounced decreases were observed in pregnancy levels of estradiol[3] and estriol[4] among women who smoked during pregnancy compared with nonsmokers. Female offspring who were prenatally exposed to cigarette smoke may be at reduced breast cancer risk as a result of lower in utero estrogen exposure.

Previous case–control studies have shown a range of associations between in utero cigarette smoke exposure and breast cancer risk.[5–8] These studies relied on either the mothers' or daughters' report of the mothers' prenatal smoking habits after the disease was diagnosed. In contrast, the National Cooperative DES Adenosis (DESAD) Project was a prospective study investigating the effects of prenatal diethylstilbestrol (DES) exposure on adverse health outcomes, including breast cancer.[9] During the recruitment phase, the mothers provided information about their experience during the index pregnancy, including their cigarette smoking habits. This article reports the results of an investigation into the association between prenatal maternal cigarette smoke exposure and breast cancer incidence based on an average of 21 years of follow up.

METHODS

Study Participants

The recruitment and follow-up procedures for the National Cooperative DES Adenosis Project have been de-

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scribed elsewhere.[9,10] Briefly, women with documented prenatal DES exposure were invited to participate in the study. From 1975 through 1981, recruitment was conducted at the following study centers: the Mayo Clinic, Rochester, Minnesota; the Gundersen Clinic, LaCrosse, Wisconsin; Baylor College of Medicine, Houston, Texas; the University of Southern California, Los Angeles, California; and the Massachusetts General Hospital, Boston, Massachusetts.

In all, 4007 women with documented prenatal exposure to DES were identified. For comparison, another 1031 women whose medical records indicated that they had no prenatal exposure to any exogenous hormones were recruited into the study. These women, some (n = 203) of whom were siblings of DES-exposed participants, were matched to DES-exposed women on birth year and maternal age. The average age at recruitment was 22.7 years (range = 9.1–39.1). From 1976 through 1983, study participants were interviewed for recent medical history at their regular gynecologic examinations. From 1984 through 1997, follow up was conducted by mailed questionnaires completed by study participants. Women who did not return a mailed questionnaire were offered a telephone interview. The data presented here reflect the follow up conducted through 1997.

Exposure and Covariate Determination

When the participants entered the study, their mothers were asked whether they smoked during the index pregnancy and, if so, the number of cigarettes smoked daily during that time. Of the 4930 participants who provided more than 1 year of follow-up information, all but 295 mothers (including 4 women whose daughters eventually developed breast cancer) provided information on cigarette smoking during the index pregnancy.

Breast cancer covariate information, including reproductive history, was updated regularly through responses to questionnaires administered during the follow-up period. Information regarding menopause was obtained only in 1994 and 1997. The analyses presented here include only women whose mothers provided smoking information and who themselves developed breast cancer or completed a questionnaire through 1994 (n = 4031). Participants who developed breast cancer are considered to have completed follow up for the disease regardless of whether they completed a questionnaire after 1994. Because the analyses presented here include only women who completed follow up through at least 1994, selective withdrawal over the course of the study may influence the study results. The overall relative effect of prenatal maternal cigarette exposure on breast cancer incidence was estimated again, including all women who provided 1 or more years of follow up regardless of whether they completed a questionnaire after 1994. There were 611 women who did not complete a questionnaire in 1994 or 1997, including 7 cases (5 who died and 2 who refused further participation). In this secondary analysis, all of these women were assumed to be premenopausal because they withdrew at an age (mean = 31.2 years) before which menopause usually occurs.

Case Identification and Ascertainment

Invasive breast cancer cases were identified from questionnaire responses or by review of available death certificates. Self-reported cases were confirmed using medical records and pathology reports obtained from the diagnosing physician. On average, the women included in this analysis were followed for 21 years. During the period between 1976 and 1997, 42 cases of invasive breast cancer were identified—all diagnosed before natural menopause. Three cases were identified by death certificate review and the remainder was self-reported. For all of the self-reported cases for which records were obtained (n = 32), the records confirmed the participant's report of a breast cancer diagnosis.

All women participating in this follow-up study provided informed consent in accordance with the policies of the Institutional Review Boards at the National Cancer Institute and the respective recruiting centers.

Statistical Analysis

Person-time accrual began at the time of enrollment into the study and ended at the earlier of the following: date of last follow up, or date of invasive breast cancer diagnosis. We used Poisson regression modeling to estimate the relative rate adjusting for the potential confounders and to calculate the associated 95% confidence intervals (CIs). Potential confounders that altered the relative rate or standard error by 0.1 or more were retained in the model. We also estimated the effect of high (>15 cigarettes/d) versus moderate exposure (1–15 cigarettes/d).

RESULTS

The profile of breast cancer covariates was similar for those who were and were not prenatally exposed to maternal cigarette smoke. We compared the percentages of women who were, themselves, active smokers (49% vs. 42%) and those for women who were nulliparous (34% vs. 33%) among the prenatally exposed and unexposed women. Women prenatally exposed to maternal cigarette smoke were the same age as those who were not (78% ≥40 years at the end of follow up). There was a higher percentage of women who were under 2500 g at birth among those whose mothers smoked while pregnant with them (16%) than among women whose mothers did not (8%). The participation rates through 1994 were similar among women who were (87%) and were not (86%) prenatally exposed to maternal cigarette smoke.

Overall, the breast cancer rate adjusted for age, parity, and active smoking among women exposed in utero to cigarette smoke was approximately half that observed among women who were not (0.49; 0.24–1.03) (Table 1). The

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TABLE 1. Relative Rates (RR) for in Utero Cigarette Smoke Exposure in Association With Breast Cancer Risk

	Cases (no.)	Person-years (no.)	Crude RR (95% CI)	Adjusted* RR (95% CI)
Any exposure	9	31,404	0.46 (0.22–0.97)	0.49 (0.24–1.03)
=15 cigarettes a day	4	19,450	0.33 (0.12–0.94)	0.35 (0.12–0.99)
>15 cigarettes a day	5	11,954	0.68 (0.26–1.73)	0.74 (0.29–1.90)
No exposure†	33	53,367	1.0	1.0

*Adjusted for age, nulliparity, and active smoking.
†Reference category.

adjusted inverse association was similar when only verified cases were considered (0.52; 0.23–1.13). When the analysis included the women who withdrew from the study before 1994, the effect estimate adjusting for potential confounding remained virtually unchanged. The associations between prenatal maternal cigarette smoke exposure and breast cancer rates specific to prenatal DES exposure were also similar. Among those who were DES-exposed, the relative rate was 0.48 (0.21–1.10), and among those who were not prenatally exposed to DES, it was 0.54 (0.11–2.62). The dose-specific effect estimates were also compared (Table 1). Relative to women with moderate prenatal cigarette smoke exposure, the breast cancer incidence among women with heavy prenatal cigarette smoke exposure was higher, although this estimate is imprecise (2.1; 0.57–7.9).

DISCUSSION

It is biologically plausible that prenatal cigarette smoke exposure may be protective against later breast cancer development. Other prenatal factors such as birth order,[11] birthweight,[2] twinning,[12] maternal age during the index pregnancy,[11,13] preeclampsia,[14] and DES exposure[15] are currently believed to be associated with maternal estrogen levels. Many, but not all, of these prenatal factors have been previously found to be associated (positively or negatively) with later breast cancer risk.[5,6,8,10,13,14,16–21]

Maternal cigarette smoking has been shown to decrease maternal estrogen levels.[2–4] Estradiol (E2) and estriol (E3) levels, however, did not decrease further with increasing amounts of cigarettes smoked.[3,4] Fetal exposure to E3 levels may be a determinant of adult breast cancer risk because, of all the estrogen subspecies, E3 reaches the highest levels in the fetal blood[4] and because moderate, but not high, late pregnancy estriol levels have been associated with increased maternal breast cancer risk.[22] In the current study, breast cancer incidence did not appear to decrease further with increasing prenatal cigarette smoke exposure. It could be speculated that relative to breast cancer rates in women with moderate prenatal cigarette smoke exposure, incidence increased with increasing number of cigarettes smoked. Possibly, genotoxic or other harmful effects of heavy cigarette smoke may override any protective effect against breast cancer associated with decreased estrogen levels. Given the small number of cases in each of the exposure categories, there may, instead, be no difference in the exposure-specific estimates.

The role, if any, that estrogen plays in mediating the association between prenatal exposure to maternal cigarette smoke and breast cancer incidence may be indirect. Pregnant women who smoked were observed to have higher serum alpha fetoprotein (AFP) levels than women who did not,[23] and AFP was observed in in vitro studies to reduce estrogen stimulation of breast cancer cell proliferation.[24] Maternal human chorionic gonadatropin (hCG) levels are reduced among smoking women.[3] Both high maternal AFP[25] and low hCG levels[3] may be indicative of reduced placental function. Maternal cigarette smoke might precipitate fetal–placental breakdown, leading to reduced transfer of maternal blood components to the fetus and possible reduction of fetal mammary epithelial cells that could be targets for tumorigenic agents in later life.

This study has some limitations. There are too few cases to allow for a precise estimation of the effect of prenatal cigarette smoke exposure and breast cancer rates. Furthermore, the dose-specific effects on breast cancer rates cannot be precisely compared due to the paucity of cases. Nonetheless, the data from this study indicate that the hypothesis of reduced breast cancer rates among women with prenatal cigarette smoke exposure warrants further consideration.

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